American Gastroenterological Association Medical Position Statement: Celiac Sprue

This document presents the official recommendations of the American Gastroenterological Association (AGA) on Celiac Sprue. It was approved by the Clinical Practice and Practice Economics Committee on September 23, 2000, and the AGA governing board on November 12, 2000.

Celiac sprue is a life-long inflammatory condition of the gastrointestinal tract that affects the small intestine in genetically susceptible individuals. The prevalence in Northern Europe is approximately 1:300, whereas in the United States it occurs less frequently. A small intestinal biopsy is mandatory to confirm the diagnosis. Treatment involves a strict gluten-free diet that excludes wheat, rye, and barley and that should be supervised by a dietician. Follow-up is important because of potential long-term complications.

Introduction

The objective is to define celiac sprue, document the prevalence, and summarize available therapy.

Celiac sprue or gluten-sensitive enteropathy is a chronic malabsorption disorder of the small intestine caused by exposure to dietary gluten in genetically predisposed individuals. The condition is characterized by villous atrophy, a lowering of the villous height to crypt depth ratio (normal, 3–5:1), an increase in intraepithelial lymphocytes (normal, 10–30 per 100 epithelial cells), and extensive surface cell damage and infiltration of the lamina propria with inflammatory cells. There are a wide range of presentations from asymptomatic through fatigue, and vague abdominal symptoms, weight loss, and diarrhea to frank malabsorption with steatorrhea. Both the symptoms and abnormal small intestinal mucosal morphology resolve on removal of gluten from the diet.

Epidemiology

The age of presentation and prevalence of celiac sprue have altered over the last 30–40 years. The condition was previously thought to be a disease of childhood. However, adult presentation is increasingly common and celiac sprue can occur at any age.

The prevalence in different countries ranges widely. Several European studies have recently revealed values between 1:152 to 1:300 in countries that include Ireland, the United Kingdom, Italy, and Sweden. Previous figures from the United States suggested that the condition affected 1:6000, however, a recent study involving serologic screening of blood donors suggested that this figure is more likely to be 1:250.

In 1997, Maki and Collin suggested the concept of the "celiac iceberg," the majority of cases going clinically undetected with either "silent" or "latent" disease. Silent celiac sprue refers to those with celiac sprue but without any symptoms, and latent celiac sprue to individuals with a normal small intestine on a normal diet but who either in the past or in the future will develop morphologic changes responsive to gluten withdrawal.

Gluten Dicke reported that the alcohol soluble fraction of wheat gluten termed gliadin is the toxic fraction contained within wheat. It was subsequently shown that the equivalent fractions of rye (secalins), barley (hordeins), and possibly oats (avenins) exacerbated celiac sprue. Several recent studies have indicated that a moderate amount of oats is not harmful in individuals with either celiac sprue or dermatitis herpetiformis. Care should be exercised because the majority of commercially available oat flour is contaminated with wheat gluten. It is therefore current practice usually to advise against the use of oats in the diet of gluten-sensitive subjects.

Genetic Predisposition

Celiac sprue is an HLA-associated condition, the primary association being with major histocompatibility complex class II alleles DQA1*0501 and DQB1*0201. This may be in *cis* in DR3-positive individuals with the DQA and DQB alleles on the same chromosome. Alternatively, they may be in trans in DR5, DR7 heterozygotes, in which the DQA and DQB alleles are on different chromosomes. In Southern Europe, there is a smaller group of individuals with susceptibility who are DR4, DQ8 heterozygotes.

Pathogenesis

Current evidence suggests that small intestinal gluten–sensitive T cells recognize gluten-derived peptide epitopes when presented in association with DQ2. The activation by the gluten of the T cells produce the observed damage to the small intestinal villous architecture that occurs in celiac sprue.

Clinical Features

Adult presentation usually involves weight loss, diarrhea, lassitude, and anemia. Children frequently present with failure to thrive, vomiting, diarrhea, muscle wasting, signs of hypoproteinemia including possible ascites, and general irritability and unhappiness.

Patients may present at any hospital department with associated conditions. One important example is insulin-dependent diabetes mellitus, in which 6%–8% of sufferers have concomitant celiac sprue. Other conditions include cerebral calcification, Sjögren syndrome, and thyroid disease. The diagnosis should be considered with unexplained folic acid, iron or B_{12} deficiency, reduced serum albumin, osteoporosis, and osteomalacia. Other presentations may include failure to grow in children, infertility, or recurrent miscarriage.

Dermatitis herpetiformis deserves special mention because it can be considered an extraintestinal manifestation of gluten-sensitive enteropathy. This manifests with a pruritic, blistering rash. The diagnosis depends on the demonstration of granular immunoglobulin (Ig) A in uninvolved skin. Treatment involves dapsone and a gluten-free diet, which, if strictly adhered to, frequently allows, after a period of 6 months, for dapsone to be withdrawn.

Serologic Markers

The main role of these tests is to screen patients who have nonspecific symptoms or an associated condition such as insulin-dependent diabetes mellitus. IgA antiendomysial antibodies are currently the best serologic test for celiac sprue with a sensitivity of 97%–100% and specificity of 98%–99%. Because 2%–3% of individuals with celiac sprue have selective IgA deficiency, IgA levels should be measured. Alternatively quantifying antigliadin antibody may be the best approach. Recently, the enzyme tissue transglutaminase has been found to be the antigen for antiendomysial antibody. This has allowed the development of a tissue transglutaminase enzyme-linked immunosorbent assay, which is reported to have a sensitivity of 95% and specificity of 94%. The sensitivity of these assays in certain commercial laboratories may not be as high as published from research centers.

Disorders of Bone Metabolism

Osteomalacia is well recognized and responds to calcium and vitamin D supplementation. Bone pain, pseudofractures, or deformity may occur, and the finding of a raised serum alkaline phosphate with normal calcium and phosphate levels may be present.

Osteopenia and osteoporosis are common features. Bone mineral density is almost always reduced. Osteoporosis carries a significant fracture risk, and thus dual energy x-ray absorptiometry (DEXA) screening of celiac sprue patients is important and now recommended. DEXA scans suggest osteoporosis if the T values obtained are less than 2.0 standard deviations below the mean values for comparable age-matched controls. If osteoporosis is found, strict adherence to a gluten-free diet should be confirmed. This may provide an indication for consideration of a repeat small intestinal biopsy in those already treated because it suggests possible poor dietary compliance. Treatment may comprise hormone replacement therapy in postmenopausal women, biphosphonates, or calcitonin. Dietary calcium supplementation up to 1500 mg/day has been recommended. Smoking should be discouraged and exercise advised. Monitoring by repeat DEXA scanning after a year allows an estimate of the rate of change of bone mineral density.

Splenic Atrophy

This occurs in celiac sprue. It has been suggested that pneumococcal immunization be administered, although whether this should be advocated for all celiac sprue patients is unknown.

Diagnosis

The mainstay of diagnosis of celiac sprue is a small intestinal biopsy specimen, which is usually taken at endoscopy. At least 3 biopsy specimens preferably should be taken with "jumbo" forceps from the distal duodenum. Some individuals, especially pediatricians, use a dedicated Watson or Crosby capsule. The characteristic changes involve damage to the normal villous morphology with decreased villous height to crypt depth, decreased epithelial surface cell height, and increased lymphocytic infiltration of the mucosa.

The generally accepted diagnostic criteria are that there should be an abnormal small intestinal mucosa while individuals continue to take a gluten-containing diet. There should then be unequivocal improvement in villous architecture on a repeat small intestinal biopsy procedure after some months on a gluten-free diet with symptomatic improvement. A repeat biopsy should usually be taken 4–6 months after induction of treatment and if there has been no improvement in the small intestinal mucosal morphology, the original diagnosis should be questioned. However, many gastroenterologists do not take a follow-up biopsy specimen and the cost-effectiveness of this approach has not be demonstrated. Most clinicians do not undertake formal gluten

challenge to show the resultant deterioration of the small intestinal villous architecture. However, gluten challenge should be performed if there is any doubt concerning the correct diagnosis.

Routine full blood count, urea and electrolytes, liver function tests, serum iron or ferritin, folate or red blood cell folate, and B_{12} should be measured at initial diagnosis. Liver function tests may be mildly abnormal in patients with celiac disease, even when associated hepatic disorders are absent. Specific deficiencies of iron and folic acid should be therapeutically corrected, although they will not normally be required long-term after introduction of a gluten-free diet. B_{12} levels usually normalize without specific therapy. A DEXA scan should be undertaken to seek evidence of osteoporosis because this usually improves on a gluten-free diet, although specific therapy may required.

Treatment

The cornerstone of treatment is a gluten-free diet. This should involve the advice of a dietician who is experienced in this field. Patients should omit wheat, rye, and barley from their diet. Oats may be permitted, although it should not be forgotten that the majority of commercially available oat flour is contaminated with wheat gluten.

It is important to explain the disease and the toxicity of gluten-containing foods to the patient. This should include information on the avoidance of future ill health or reversal of current problems including anemia, depression, and infertility. Explaining the increased risk of malignancy, particularly small intestinal lymphoma, is debatable and should be decided with discretion on a patient-by-patient basis. Physicians should not frighten patients into dietary compliance but provide them with the necessary facts for them to decide themselves.

It is advisable for patients to join a celiac sprue group that usually publishes lists of locally available gluten-free products. There are now a wide range of gluten-free breads, biscuits, "pasta," etc. that are commercially available in the United States and many European countries, where they can be obtained on a prescription. Specific foods that require some mention include beer and malted breakfast cereals, which should be avoided because they contain celiac toxic barley hordein. Patients with celiac sprue usually experience a rapid symptomatic improvement within a matter of weeks of the exclusion of dietary gluten, and this provides additional diagnostic confirmation.

Nutrient Deficiency

At the time of diagnosis, routine blood tests including full blood count and biochemical profile (which includes albumin concentration, ferritin, serum folate or red cell, and B_{12}) should be measured. Supplements to replace iron and folate and B_{12} may be required if reduced serum levels of ferritin and folate are found, although levels frequently correct on treatment with a gluten-free diet. Monitoring of antiendomysial or tissue transglutaminase antibody titers, which usually normalize with the institution of a gluten-free diet, may prove useful to check dietary compliance. Occasionally, calcium and vitamin D supplementation may be required. Similarly, life-threatening hypokalemia or hypomagnesemia may occur and should be appropriately corrected.

Nonresponsive Celiac Sprue

The most common cause of nonresponsiveness is continued gluten intake. Should the biopsy remain abnormal, a wheat-free, gluten-free diet should be initiated in which there is avoidance of wheat starch–based gluten-free foods in addition to the standard gluten-free diet. It is important to stress that clinicians should rule out other treatable diseases with similar histology that do not respond to a gluten-free diet.

Steroids can be used, and an acute crisis is managed with parenteral hydrocortisone. Oral corticosteroids may be used in nonresponsive disease but only when other causes of small intestinal villous atrophy have been excluded. 6-Mercaptopurine or azathioprine may be used as steroid-sparing agents if a dose of more than 10 mg/day of prednisolone is required.

Ulcerative Jejunitis

In this condition, there are ulcers affecting the jejunum or ileum. Scarring can lead to stricture formation with intervening areas of dilated bowel. There is a variable degree of villous atrophy in adjacent and distant mucosa. There is a high mortality rate with death often following hemorrhage, perforation, or obstruction possibly on a background of malnutrition. Diagnosis can be difficult, with small intestinal radiology often being unhelpful. If ulceration or lymphoma beyond the second part of the duodenum is thought likely, enteroscopy may be useful to obtain biopsy specimens for histologic assessment.

Surgical resection of the ulcer, especially if localized to one part of the intestine, can be curative. Stricturoplasty may be undertaken. A strict gluten-free diet should be initiated, and steroids are often used, sometimes with

benefit. If a diagnosis of enteropathy-associated T-cell lymphoma is made, the patient should be referred to an oncologist for appropriate chemotherapy.

Malignancy

There is an increase in overall mortality in celiac sprue. The excess deaths are mainly caused by malignancy, the majority of which involve intestinal lymphoma. Holmes and colleagues found a 5-fold increased risk of developing malignancy in a celiac population with a relative risk of developing non-Hodgkin lymphoma of 40. This risk fell to the level of the normal population after patients had taken a gluten-free diet for 5 years.

Small bowel radiology, enteroscopy, and a computer-aided tomographic radiographic scanning should be undertaken if lymphoma is suspected. Laparotomy may be required. Treatment for enteropathy-associated T-cell lymphoma is unsatisfactory with a low survival rate. After lymphoma, the most common malignancy is adenocarcinoma of the intestine. Presentation may involve anaemia, gastrointestinal blood loss, weight loss, obstruction, vomiting, and abdominal pain.

Follow-up

Some physicians contend that after introduction of a gluten-free diet, most patients remain well. It is generally advocated that yearly weight, full blood count, ferritin, folate, calcium, and alkaline phosphatase should be recorded. Follow-up should be life-long, and this permits reinforcement of the continuing need for strict adherence to the gluten-free diet.

Screening first degree relatives may be undertaken and other associated conditions may be sought in affected individuals. It is wise, therefore, that follow-up should be undertaken by a physician.

Suggested Reading

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Additional Information

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